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The association between atherosclerotic risk factors and renal function in the general population

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Background. Generalized atherosclerosis is increasingly recognized as an important cause of end-stage renal disease (ESRD). We questioned to what extent atherosclerotic risk factors determine renal function in the general population.

Methods. We used baseline data of the Prevention of Renal and Vascular End-Stage Disease (PREVEND) Study. A total of 8592 subjects, aged 28 to 75 years old, visited the outpatient clinic for blood pressure and anthropometric measurements, fasting blood sampling, and delivery of two 24-hour urine collections for creatinine clearance and albuminuria calculations. Design-based multivariate linear regression was used to estimate renal function.

Results. In a multivariate model, male gender and body mass index (BMI) were associated with a higher renal function, while increasing diastolic blood pressure, serum triglycerides, use of antihypertensive or lipid-lowering medication were associated with a lower renal function. Age, systolic blood pressure, and plasma glucose showed an inverse U-shaped relationship with renal function. Cholesterol/high-density lipoprotein (HDL) ratio, smoking, and antidiabetic medication did not contribute to explain renal function. The atherosclerotic risk factors were related to renal function independently of albuminuria or C-reactive protein (CRP). Albuminuria and CRP itself were also related to renal function. Following gender and age, BMI, urinary albumin excretion (UAE), and plasma glucose had the strongest relation with renal function.

Conclusion. We conclude that differences in renal function in the general population are (partly) explained by various atherosclerotic risk factors. Some risk factors are associated with elevated filtration, some with an impaired filtration, and others with both a higher and a lower renal function.

Key words: renal function, creatinine clearance, cardiovascular risk factors, PREVEND.

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The incidence of end-stage renal disease (ESRD) is increasing, and the number of patients on renal replacement therapy is growing steadily [1, 2]. In the past, ESRD was mainly due to primary renal diseases such as glomerulonephritis and pyelonephritis or interstitial nephritis, while presently ESRD is mostly due to type 2 diabetic nephropathy and generalized atherosclerosis. In fact, diabetes, hypertension and renovascular disease are the main causes of ESRD [2–4].

Besides hypertension and increased glucose other atherosclerotic risk factors, such as hyperlipidemia, obesity and smoking may also have impact on renal function, even when no underlying kidney disease is present [3, 5–7]. In addition, markers of generalized atherosclerosis, such as an elevated urinary albumin excretion (UAE) [8–10] and an elevated C-reactive protein (CRP) [11, 12], have been found to be independently associated with renal function [13–17]. Because the various risk factors can be influenced by counseling and/or active treatment, it is of importance to know how and to what extent these atherosclerotic risk factors are related to renal function in the general population. A number of epidemiologic studies related specific risk factors to renal function; however, only a few looked at an integral approach. These were furthermore performed either in a specific population [18] or taking into account only a selection of risk factors [3]. We therefore undertook an integral approach at investigating first the association of various atherosclerotic risk factors, with renal function in the general population. Second, we tested whether these associations are mediated via their relation with albuminuria and CRP.

METHODS

Study design and population

We used the baseline data of the 8592 subjects of the Prevention of Renal and Vascular End-stage Disease (PREVEND) Study cohort. The PREVEND Study aims

to investigate the impact of UAE on renal and cardiovascular disease in the general population. In this study all inhabitants of the city of Groningen, The Netherlands, in the range of 28 to 75 years old ($N = 85,421$), were invited to answer a short questionnaire and to collect a morning spot urine. A total of 40,856 spot urine samples were tested for urinary albumin concentration (UAC). Responders were less likely to be male than nonresponders (45.6% versus 54.6%) and had a younger age (49.5 years versus 51.9 years), but the prevalence of risk factors in our cohort was in general reasonable comparable to the national prevalence (hypertension 11.2% versus 8.4%; diabetes 2.6% versus 2.1%; smoking 42.2% versus 31.5%; previous myocardial infarction 3.4% versus 2.5%; and previous cardiovascular accident 0.8% versus 0.6%). After exclusion of pregnancy and subjects using insulin, all subjects with a UAC of ≥10 mg/L ($N = 7768$) and a control group with UAC <10 mg/L (3395) were invited twice to an outpatient clinic. Subjects filled in an extended questionnaire giving demographics, cardiovascular and renal history, smoking status, and the use of oral antidiabetic, antihypertensive and antilipidemic drugs, and collected two 24-hour urine samples on 2 consecutive days. We measured weight, height, and took fasting blood samples. Blood pressure was automatically measured (Dinamap XL Model 9300 series device) (Johnson-Johnson Medical, Inc., Tampa, FL, USA) during 10 minutes on both visits. Together, 8592 subjects completed both visits. For the present study we excluded 451 subjects because of leucocyturia or erythrocyturia, according to dipstick analysis (leukocytes >75/μL or erythrocytes >50/μL, or leukocytes = 75 and erythrocytes >5/μL), which makes the albumin measurement unreliable. Another 72 subjects were excluded because they indicated by questionnaire as having a primary renal disease. This left 8069 subjects for the present analyses. All subjects gave written informed consent. The local medical ethics committee approved the PREVEND Study and the conduct of the project was in accordance with the guidelines of the declaration of Helsinki.

Measurements and definitions

Body mass index (BMI) was calculated as weight (kg) divided by square of height (m^2). Blood pressure values given are the mean of the last two recordings of both days. Smoking was defined as current smoking or cessation of smoking less than a year before the study. Triglycerides were measured enzymatically. Creatinine assessments in blood and urine, serum cholesterol, and glucose were determined by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY, USA), an automatic enzymatic method. A commercially available assay system was used to assess high-density lipoprotein (HDL) (Abbott Inc., Abbott Park, IL, USA). The intra- and interassay variation coefficient of serum creatinine was 0.86% and 1.11%, respectively. For urinary creatinine the coefficients were 0.90% and 2.90%, respectively. Renal function is measured as creatinine clearance, which is given as the mean of two 24-hour urinary creatinine excretions divided by plasma creatinine. Urinary leukocyte and erythrocyte measurements were done by Nephurtest + leuco sticks (Boehringer Mannheim, Mannheim, Germany). UAC was determined by nephelometry with a threshold of 2.3 mg/L and intra- and interassay coefficients of variation of less than 2.2% and 2.6%, respectively (Dade Behring Diagnostic, Marburg, Germany). UAE is given as the mean of the two 24-hour urine excretions. High sensitive CRP was also determined by nephelometry (threshold 0.175 mg/L and intra- and interassay coefficient of 4.4% and 5.7%, respectively).

Statistical analyses

The null hypothesis tested was no trend of the variable of interest over the quintiles of creatinine clearance (General Linear Model). A chi-square test was applied to investigate if the number of males, smokers, and subjects using medication had a linear trend over the quintiles of creatinine clearance.

To be able to study the impact of albuminuria in the general population, subjects with elevated UAC were oversampled in the PREVEND Study cohort. We used design-based linear regression using weighing factors to correct for the oversampling of subjects with an elevated UAE [19] (STATA, Texas version 8.0). For the analyses in the present study the response variable of the multivariate linear regression model was creatinine clearance. Predictor variables included in the regression model were gender, age, systolic and diastolic blood pressure, BMI, plasma glucose, serum cholesterol/HDL ratio, serum triglycerides, smoking, the use of antihypertensive, lipid-lowering, or antidiabetic medication, and CRP and UAE. Medication use was entered in the regression model because risk factors as blood pressure, lipids, or glucose could be altered because of the use of medication.

Visual inspection of the data revealed a curved relationship between creatinine clearance and some of the explanatory variables. Examination of the curvature was done by graphic interpretation, and by including a quadratic term of the variable in the linear regression model. For optimal residual analysis UAE, plasma glucose, triglycerides, and CRP were transformed by a natural logarithm. A two-tailed P value of < 0.05 was considered significant. The comparison between two models with more than one degree of freedom was done by an adjusted Wald test [20]. The analyses were repeated after validation for urinary collection errors, by exclusion of subjects with >20% difference in urinary creatinine excretion between the two 24-hour urine collections, and

Table 1. Population characteristics according creatinine clearance (mL/min) in quintiles

	Creatinine clearance in quintiles					Total population	*P* value for trend quintiles
	1	2	3	4	5		
Creatinine clearance (mL/min)	69.0 (11.3) (<81.7)	88.7 (3.9) (81.7–95.3)	101.8 (3.8) (95.3–108.3)	115.6 (4.4) (108.3–123.8)	142.2 (18.5) (>123.8)	103.5 (26.7)	
Number of subjects	1592	1592	1593	1592	1592	7961	
Men%	32.8	36.0	48.6	62.9	78.4	51.7	<0.001[a]
Age *years*	55 (13)	50 (13)	48 (12)	46 (12)	45 (10)	49 (13)	<0.001[a]
Systolic blood pressure *mm Hg*	132 (25)	127 (20)	127 (19)	128 (19)	131 (17)	129 (20)	<0.001[b]
Diastolic blood pressure *mm Hg*	74 (10)	73 (9)	74 (10)	74 (10)	75 (9)	74 (10)	<0.001[b]
Body mass index kg/m^2	25.5 (4.2)	25.3 (3.9)	25.6 (3.9)	26.2 (4.0)	27.8 (4.7)	26.1 (4.2)	<0.001[a]
Cholesterol *mmol/L*	5.8 (1.2)	5.6 (1.1)	5.6 (1.2)	5.6 (1.1)	5.6 (1.1)	5.6 (1.1)	<0.001[a]
High-density lipoprotein *mmol/L*	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)	1.3 (0.4)	1.2 (0.3)	1.3 (0.4)	<0.001[a]
Cholesterol/high-density lipoprotein ratio	4.5 (1.7)	4.4 (1.7)	4.5 (1.7)	4.8 (1.8)	5.1 (2.0)	4.7 (1.8)	<0.001[a]
Triglycerides *mmol/L*	1.2 (0.9–1.7)	1.1 (0.8–1.6)	1.1 (0.8–1.7)	1.2 (0.8–1.7)	1.2 (0.7–1.8)	1.2 (0.8–1.7)	<0.001[b]
Glucose *mmol/L*	4.8 (1.2)	4.8 (1.2)	4.9 (1.3)	4.9 (1.1)	5.1 (1.2)	4.9 (1.2)	<0.001[a]
Smoking%	37.3	37.6	37.4	38.0	38.4	37.7	0.492
Antihypertensive medication%	19.2	10.6	10.2	9.5	9.0	11.7	<0.001[a]
Lipid-lowering medication%	9.4	5.7	5.7	5.3	4.0	6.0	<0.001[a]
Antidiabetic medication%	2.5	1.3	1.7	1.1	1.8	1.7	0.094[b]
C-reactive protein *mg/L*	1.5 (0.7–3.4)	1.1 (0.5–2.7)	1.2 (0.5–2.8)	1.1 (0.5–2.6)	1.3 (0.6–3.1)	1.3 (0.6–2.9)	<0.001[b]
Urinary albumin excretion *mg/24 hours*	7.5 (5.1–17.2)	7.9 (5.7–14.2)	8.8 (6.3–15.6)	9.6 (6.7–16.8)	11.5 (8.1–20.8)	9.2 (6.2–17.1)	<0.001[a]

A total of 673 subjects had missing information on one of the variables included in the regression model.

The mean and standard deviation is given enclosed in parentheses, except for triglycerides, urinary albumin excretion, and C-reactive protein, which are expressed as median with 25th and 75th percentiles enclosed in parentheses and creatinine clearance as median, SD, and the range enclosed in parentheses.

[a] *P* value for linear trend; [b] *P* value for quadratic trend.

by using indirect renal function estimates, such as the Cockcroft-Gault and simplified Modification of Diet in Renal Disease (MDRD) formula. In addition these analyses were repeated after exclusion of diabetic subjects.

RESULTS

Table 1 shows the characteristics of the population, when subdivided into quintiles according to creatinine clearance. In the highest compared to the lowest quintile of creatinine clearance, more subjects were male, had higher BMI, plasma glucose, and UAE. A U-shaped relation was shown for systolic blood pressure, diastolic blood pressure, serum triglycerides, and CRP. In the lowest quintiles of creatinine clearance subjects had higher age, serum total cholesterol and HDL cholesterol, but a lower total cholesterol/HDL ratio. The subjects in the lowest quintile also used more frequently antihypertensive and lipid-lowering medication. Over every quintile of creatinine clearance a similar number of smokers was present. No pattern was observed in antidiabetic medication use over the quintiles of creatinine clearance. Univariately, the following variables, besides age and gender, were associated with creatinine clearance: BMI, systolic blood pressure, glucose, antihypertensive and lipid-lowering medication, cholesterol/HDL ratio, triglycerides, and diastolic blood pressure as was UAE.

The atherosclerotic risk factors BMI, systolic blood pressure, diastolic blood pressure, glucose, triglycerides as well as the use of antihypertensive and lipid-lowering medication, were also in multivariate analyses independently associated with creatinine clearance ($r^2 = 0.31$) (Table 2, model 1). Total cholesterol/HDL ratio, smoking, and antidiabetic medication were not associated with creatinine clearance. As presented in the multivariate model (Table 2, model 1), male gender and higher BMI were associated with a higher creatinine clearance, whereas higher diastolic blood pressure, serum triglycerides, and antihypertensive and lipid-lowering medication were associated with a lower creatinine clearance. Higher age was also negatively associated with creatinine clearance, however, in a curvature relation. The use of antihypertensive and lipid-lowering drugs was associated with a 3.5 and 5.1 mL/min lower creatinine clearance. The association between, respectively, systolic blood pressure, and plasma glucose versus creatinine clearance was an inverse U-shaped curve. To study if the relation of cardiovascular risk factors and renal function was mediated by UAE or CRP, these factors were added to the regression model (Table 2, model 2). The beta coefficients of the cardiovascular risk factors hardly changed which indicates that the link between risk factors and renal function is independent of UAE and CRP. UAE itself also showed an inverse U-shaped relation with renal function and the association between CRP and renal function was negative.

In Figure 1 the association between the atherosclerotic factors and renal function is visualized. In the multivariate model the ranking order of the variables (starting with strongest F test) was shown in Table 3, model 1. Table 3, model 2 shows the ranking order after inclusion of UAE and CRP in the multivariate model. Starting with the highest ranking, the ranking order of strength was gen-

Table 2. Design based multivariate regression model of atherosclerotic risk factors/markers and creatinine clearance as dependent variable (model 1 is atherosclerotic risk factors and model 2 is atherosclerotic risk factors and markers)

	Model 1				Model 2			
	$R^2 = 0.31$ Beta coefficient	$N = 7689$ Standard error	*P* value	*P* value (Wald statistic)[a]	$R^2 = 0.39$ Beta coefficient	$N = 7396$ Standard error	*P* value	*P* value (Wald statistic)[a]
Gender[b]	17.85	0.76	<0.001		16.14	0.74	<0.001	
Age	0.45	0.24			0.56	0.23		
Age^2	−0.01	2.35×10^{-3}		<0.001	−0.01	2.25×10^{-3}		<0.001
Body mass index	1.71	0.12	<0.001		1.73	0.11	<0.001	
Systolic blood pressure	0.59	0.16			0.54	0.15		
Systolic blood pressure^2	-1.86×10^{-3}	0.54×10^{-3}		0.007	-1.89×10^{-3}	0.52×10^{-3}		0.001
Diastolic blood pressure	−0.14	0.06	0.016		−0.18	0.06	0.001	
Ln glucose	68.53	11.99			71.34	11.68		
Ln glucose^2	−13.83	3.31		<0.001	−15.20	3.29		<0.001
Antihypertensive medication[c]	−3.51	1.25	0.005		−3.27	1.20	0.007	
Lipid-lowering medication[c]	−5.07	1.48	<0.001		−5.07	1.35	<0.001	
Ln Triglycerides	−4.06	0.76	<0.001		−3.26	0.72	<0.001	
Ln urinary albumin excretion					34.53	1.91		
Ln urinary albumin exretion^2					−4.74	0.30		<0.001
Ln C-reactive protein					−0.70	0.33	0.033	
Intercept	−11.64	15.87			−58.5	15.07		

[a]Composite variables tested by adjusted Wald test.
[b]Reference group of gender is female gender.
[c]Reference group of lipid-lowering or antihypertensive medication is non-users.

der, age, BMI, UAE, plasma glucose, serum triglycerides, lipid-lowering medication, diastolic blood pressure, antihypertensive medication, systolic blood pressure, and CRP. BMI lost its high ranking when renal function was corrected for body surface area (BSA).

The multivariate analysis was repeated after validation for collection errors; exclusion of subjects with >20% difference in urinary creatinine excretion between the two 24-hour urine collections. We also repeated the analyses by using other GFR estimates (Cockcroft-Gault and the simplified MDRD formulas). These additional analyses did not change the above-presented results. Analyzing the linear model explaining BSA corrected creatinine clearance, lowered the beta coefficient of gender and BMI (to 5.3 and 0.3, respectively) as compared with non-BSA correction. However, the other coefficients did not change substantially. The direction of the associations between the atherosclerotic factors and renal function did not change after exclusion of subjects using antihypertensive, lipid-lowering medication, or subjects with diabetes.

DISCUSSION

We found that several atherosclerotic risk factors explain the variation in renal function in this large cohort study. The impact of the individual factors (analyzed in a multivariate setting) varied considerably. Some factors had a straight linear impact, others interestingly showed a parabolic or hyperbolic function relation, meaning that different levels of the explaining parameter had a different relation with renal function. Moreover, the pathogenetic pathway relating atherosclerotic risk factors with renal function seems to be independent of albuminuria or low grade inflammation.

Intervention in these factors, such as life style advices or drug prescription, can ameliorate the risk factors and may thus be favorable for renal function. As albuminuria was one of the factors most strongly associated with renal function, the present data may encourage clinicians to test for UAE in patients with atherosclerotic risk factors.

These presentations of data are new when compared to those studies that focused on the relation of renal function and one atherosclerotic risk factor. We investigated the integral relation of a number of established atherosclerotic risk factors to determine the factors with the largest impact on renal function as a continuous parameter, whereas other studies classify renal function into groups which gives no information on the shape of the relation of atherosclerotic risk factors and renal function.

As expected, we found men to have a higher creatinine clearance than women, and older subjects to have a lower creatinine clearance. The age-related decline in renal function is caused most likely by an involutional process. It is known from literature that some subjects show no change in renal function over the years, whereas in others a manifest decline is observed, suggesting that the impact of subclinical atherosclerotic pathology may be more prominent in one subject than the other [21].

We showed a positive association of BMI and creatinine clearance, which was still present after correction of renal function for BSA. These findings are comparable with other reports in literature that show an elevated GFR in obese subjects [22, 23]. Hyperfiltration is hypothesized to be the underlying mechanism of obesity related

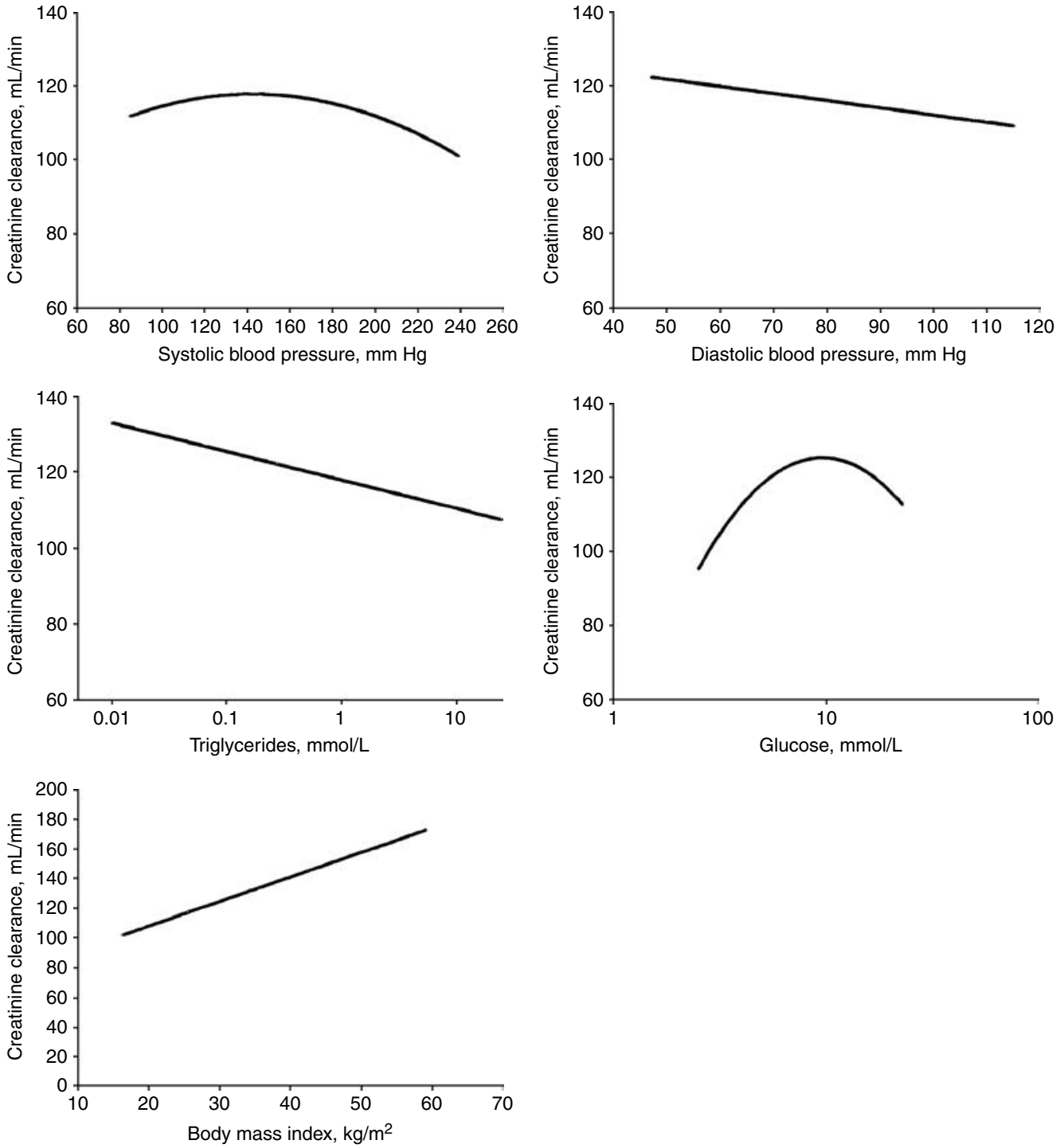

Fig. 1. Figures of the relation of cardiovascular risk factors and renal function. The equation of the regression model is graphed by using the median for the covariates, male gender and no medication use.

renal failure [6]. In obese Zucker rats glomerular injury correlated with hyperphagia-induced glomerular hyperfiltration which could be prevented by food restriction [24]. In a previous study we showed that especially an abdominal fat distribution is associated with a diminished filtration [25].

Haroun et al [26] showed that high-normal blood pressure is associated with increased risk of developing chronic kidney disease in a community-based cohort. Also in a cross-sectional analysis of the NHANES III population, higher systolic and diastolic blood pressure and the presence of hypertension were associated with

Table 3. F test of strength of the association between atherosclerotic risk factors/markers and creatinine clearance (model 1 is atherosclerotic risk factors and model 2 is atherosclerotic risk factors and markers)

		Model 1			Model 2		
	df (numerator)	F test	*P* value	Ranking order	F test	*P* value	Ranking order
Gender	1	548.6	<0.001	1	482.0	<0.001	1
Age	2	345.6	<0.001	2	355.3	<0.001	2
Body mass index	1	217.4	<0.001	3	228.7	<0.001	3
Ln glucose	2	52.8	<0.001	4	51.2	<0.001	5
Ln triglycerides	1	28.8	<0.001	5	20.7	<0.001	6
Lipid-lowering medication	1	11.8	<0.001	6	14.1	<0.001	7
Systolic blood pressure	2	7.3	<0.001	7	6.6	0.001	10
Antihypertensive medication	1	7.9	0.005	8	7.3	0.007	9
Diastolic blood pressure	1	5.8	0.016	9	10.4	0.001	8
Ln urinary albumin excretion	2				188.2	<0.001	4
Ln C-reactive protein	1				4.5	0.033	11

higher serum creatinine levels [27]. In our study systolic blood pressure had an inverse U-shaped association with creatinine clearance, and diastolic blood pressure a negative association. This remarkable observation might indicate that the relation of blood pressure and renal function is not straight forward. Longitudinal data are required to explore if blood pressure alters renal function or if the relation is predominantly the inverse. An inverse U-shaped pattern was also observed for UAE and plasma glucose in relation to renal function which indicated that it may be possible that the different levels of UAE or plasma glucose are not in the same way related to renal function. Another possibility is that certain unmeasured confounding effects cause these nonlinear relations. Obesity, high blood pressure, high fasting glucose, and microalbuminuria (elevated UAE) are determinants of the metabolic syndrome and their interaction leads to chronic cardiovascular diseases and possibly also to kidney diseases [28, 29]. Combined action of risk factors of the insulin resistance syndrome may be detrimental for renal function.

Triglycerides had a negative association with creatinine clearance. Cholesterol/HDL ratio was positively associated to renal function; however, this relation was not independent of triglycerides. The ARIC study showed in a population-based sample in the United States that low HDL cholesterol and hypertriglyceridemia increase the risk of renal function loss [5, 30]. Dyslipidemia was also in the Physicians' Health Study associated with an increased risk of developing renal dysfunction [5].

As we described previously, CRP was associated with a diminished filtration [31]. In this study CRP and renal function were furthermore on the entire level of creatinine clearance negatively related. This finding is in contrast with longitudinal data of the MDRD Study, which reported that CRP was not an independent risk factor for progression of nondiabetic kidney disease in patients with preexisting renal disease [32]. The difference may be due to the fact that we analyzed subjects from the general population, whereas the MDRD Study was performed in patients with renal disease. Although we previously described an association between smoking and both hyperfiltration and diminished filtration [33], smoking was not related to creatinine clearance on a continuous scale.

A limitation of the present study is the fact that we measured renal function as the clearance of creatinine instead as clearance of specific glomerular filtration rate (GFR) tracers, such as inulin or iothalamate. Performance of renal function studies with such tracers in a population study with the size of the current study is, however, neither feasible nor ethical. Many population studies use formulas to estimate GFR based on a single serum creatinine measurement. These formulas have their limitations based on their generalizability to different populations [34]. The use of creatinine clearance in this study is therefore an advantage, especially because we used the mean of two 24-hour creatinine clearances. This minimizes the error caused by incomplete urine collection. We also examined the robustness of our findings by excluding subjects with a more than 20% difference in urinary creatinine excretion between the 2 days. A second validation of renal function estimation was performed by using either Cockcroft-Gault and MDRD estimated clearances. Essentially the same results were observed by using these validations of renal function. A second limitation of our study is its cross-sectional character. We cannot conclude that the parameters associated with either a higher or a lower creatinine clearance indeed are causally related to creatinine clearance. Neither can we conclude that treatment of the risk factor will prevent creatinine clearance to become abnormal. The ongoing follow-up of the PREVEND cohort may give answers to these questions. A strength of this study is that by using weighing factors in a design-based linear regression model, the presented results are generalizable to the general population.

CONCLUSION

In the general population renal function is related to most of the atherosclerotic risk factors, such as plasma glucose, BMI, blood pressure, triglycerides, and the use

of antihypertensive or lipid-lowering medication. In addition, it is strongly associated with two novel markers of vascular damage, albuminuria and CRP. The relation of cardiovascular risk factors and renal function is however, not mediated by albuminuria or CRP.

Some of the cardiovascular risk factors are associated with a higher and some with a lower renal function. Intervention in the cardiovascular risk factors and monitoring albuminuria may contribute to the prevention of renal function impairment in an early stage.

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